

X15642.ST25.txt SEQUENCE LISTING

<110> Eli Lilly and Company <120> MODIFIED GLUCAGON-LIKE PEPTIDE-1 ANALOGS <130> X-15642 <140> us 10/516,490 <141> 2003-06-02 24 <160> <170> PatentIn version 3.3 <210> 1 31 <211> <212> PRT <213> Artificial <220> <223> Synthetic constructs <220> <221> <221> <222> <223> MISC_FEATURE (1)..(1)Xaa= L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, beta-hydroxyhistidine, homohistidine, alpha-fluoromethyl-histidine, or alpha methyl-histidine <220> <221> <222> MISC_FEATURE (2)..(2) <223> Xaa= Ala. Glv. Val. Leu. Ile. Ser. or Thr <220> <221> <222> MISC_FEATURE <223> Xaa= Phe, Trp, or Tyr <220> <221> <222> <223> MISC_FEATURE (10)..(10) Xaa= val, Trp, Ile, Leu, Phe, or Tyr <220> <221> <222> <223> MISC_FEATURE (12)..(12) Xaa= Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val <220> <221> MISC_FEATURE <222> (13)..(13) Xaa= Tyr, Trp, or Phe <223> <220> <221> MISC_FEATURE <222> (14)..(14)<223> Xaa= Leu, Phe, Tyr, or Trp <220>

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2-amino-histidine, beta-hydroxy-
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Xaa = Gly, Pro, Ser, L-Cys, D-Cys, homocysteine, or penicillamine
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x15642.ST25.txt
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Amidation
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MOD_RES

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X15642.ST25.txt
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         Amidation
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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or is absent
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NH2, or is absent
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       (37)..(37)
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       (38)..(38)
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or is absent
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or is absent

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Xaa = Ser, His, Pro, Lys, Arg, L-Cys, D-Cys, homocysteine, penicillamine, NH2

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Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Xaa Gly Xaa Xaa Xaa Xaa Xaa 30
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2-amino-histidine, beta-hydroxy-
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Xaa = Gly, Glu, Asp, or Lys
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Xaa = Val or Ile
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        Xaa = Pro, Ala, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
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        (38)..(38)
        Xaa = Pro, Ala, Arg, Lys, His, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or is absent
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        Xaa = His, Ser, Arg, Lys, L-Cys, D-Cys, homocysteine,
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X15642.ST25.txt
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Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Lys Gly Gly Pro Xaa
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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        Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
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X15642.ST25.txt
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        or is absent
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       Xaa = Pro, Ala, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
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        is absent
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       Xaa = Ser, His, Ser-NH2, His-NH2, L-Cys, D-Cys, homocysteine,
        penicillamine, NH2 or is absent
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        (45)..(45)
        Xaa = L-Cys, D-Cys, homocysteine, penicillamine, NH2 or is absent
<223>
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Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Xaa Gly Xaa Xaa Xaa
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       Artificial
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       Synthetic construct
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       (32)..(32)
<223>
       Xaa = Ser, Pro, or His
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       (33)..(33)
Xaa = Ser, Arg, Thr, Trp, or Lys
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Xaa = Ser or Gly
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       (35)..(35)
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       Xaa = Ala, Asp, Arg, Glu, Lys, or Gly
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       Xaa = Pro, Ala, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
       is absent
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       Xaa = Pro, Ala, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
       is absent
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       (38)..(38)
       Xaa = Pro, Ala, Arg, Lys, His, NH2, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
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<220> <221>

<222>

MISC_FEATURE

(39)..(39)

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X15642.ST25.txt
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       Xaa = Ser, His, Pro, Lys, Arg, Gly, L-Cys, D-Cys, homocysteine,
        penicillamine, NH2, or is absent
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        (40)..(40)
        Xaa = His, Ser, Arg, Lys, Pro, Gly, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
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       Xaa´= His´, Ser, Arg, Lys, L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is absent
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        MISC_FEATURE
       (42)..(42)
Xaa = Gly, His, L-Cys, D-Cys, homocysteine, penicillamine, HN2,
<222>
<223>
        or is absent
<220>
<221>
        MISC_FEATURE
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       (43)..(43)
Xaa = Pro, His, L-Cys, D-Cys, homocysteine, penicillamine, NH2 or
<223>
        is absent.
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Xaa = Ser, His, Ser-NH2, His-NH2, L-Cys, D-Cys, homocysteine,
penicillamine, NH2, or is absent
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        Xaa = L-Cys, D-Cys, homocysteine, penicillamine, NH2, or is
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        absent
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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Gly Pro Xaa
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        Artificial
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        Synthetic construct
<220>
<221>
        MISC_FEATURE
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2-amino-histidine beta-hydroxy-
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         histidine, homohistidine, alpha-fluoromethyl-histidine, or alpha-methyl-histidine
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Xaa = Ala, Gly, Val, Leu, Ile, Ser, or Thr
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         Xaa - Phe, Trp, or Tyr
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         (12)..(12)
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         Xaa = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val
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Xaa = Ala, Val, Ile, or Leu
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         (21)..(21)
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         (24)..(24)
Xaa = Ala or Glu
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Xaa = Val or Ile
```

<223> <400>

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x15642.ST25.txt
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Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Lys Gly Arg Lys
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        2-amino-histidine, beta-hydroxy-
        histidine, homohistidine, alpha-fluoromethyl-histidine, or
        alpha-methyl-histidine
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Xaa = Val, Phe, Tyr, or Trp
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        (12)..(12)
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        Xaa = Ser, Tyr, Trp, Phe, Lys, Ile, Leu, or Val
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Xaa = Gly, Glu, Asp, or Lys
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        (19)..(19)
Xaa = Ala, Val, Ile, or Leu
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(27)..(27)
Xaa = Val or Ile
<222>
<223>
<400>
xaa Xaa Glu Gly Thr Phe Thr Ser Asp Xaa Ser Xaa Tyr Leu Glu Xaa
Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Lys Gly Arg Lys
```

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<213>
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        xaa = L-histidine, D-histidine, desamino-histidine,
2-amino-histidine, beta-hydroxy-
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        (12)..(12)
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        Xaa = Tyr, Trp, or Phe
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        Xaa = Leu, Phe, Tyr, or Trp
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Xaa = Gly, Glu, Asp, or Lys
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Xaa = Ala, Val, Ile, or Leu
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xaa = Glu, Ile, or Ala
<223>
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       Xaa = Val or Ile
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        (34)..(34)
<223> Xaa = Ser, Gly, Lys, NH2 or is absent
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<223> Xaa = Pro, Ala, Lys, NH2 or is absent
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<222> (37)..(37)
<223> Xaa = Pro, Ala, Lys, NH2 or is absent
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<221> MISC_FEATURE <222> (38)..(38)
<223> Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
<220>
<221> MISC_FEATURE .
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       (39)..(39)
```

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x15642.ST25.txt
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        Xaa = Ser, His, Pro. Lvs. Arg, NH2 or is absent
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        (41)..(41)
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        Xaa = His, Ser, Arg, Lys, NH2, or is absent
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       Xaa = Lys, NH2, or is absent
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Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Xaa Gly Xaa Xaa Xaa
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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        (1)...(1)
       Xaa = L-histidine, D-histidine, desamino-histidine,
2-amino-histidine, beta-hydroxy-
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       Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
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<221>
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       (16)...(16)
<223>
       Xaa = Glv. Glu. Asp. or Lvs
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x15642.ST25.txt
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<221> MISC_FEATURE
<222> (27)..(27)
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      Xaa = Val or Ile
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<223> Xaa = Lvs. Asp. Arg. or Glu
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<221> MISC_FEATURE <222> (31)..(31)
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       (32)..(32)
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<221> MISC_FEATURE
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<223> Xaa = Ser, Gly, Lys, NH2 or is absent
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      Xaa = Ala, Asp, Arg, Glu, Lys, Gly, NH2 or is absent
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      (37)..(37)
<223> Xaa = Pro, Ala, Lys, NH2, or is absent
<220>
<221> MISC_FEATURE
<222>
      (38)..(38)
<223>
     Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
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Xaa = Ser, His, Pro, Lys, Arg, NH2 or is absent Page 21

<220> <221>

<222>

<223>

MISC_FEATURE

(39)..(39)

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<220>
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         (41)...(41)
        Xaa = His, Ser, Arg, Lys, NH2 or is absent
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         (42)..(42)
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        Xaa = Lys, NH2, or is absent
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Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Xaa Gly Xaa Xaa Xaa
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        Xaa = L'histidine, D-histidine, desamino-histidine,
2-amino-histidine, beta-hydroxy-histidine, homohistidine,
alpha-fluoromethyl-histidine, or alpha-methyl-histidine
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         (2)..(2)
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Xaa = Gly, Glu, Asp, or Lys
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        (19)..(19)
Xaa = Ala, Val, Ile, or Leu
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         (27)..(27)
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X15642.ST25.txt
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       Xaa = Ser, Arg, Thr, Trp, Lys, NH2 or is absent
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       (34)..(34)
Xaa = Ser, Gly, Lys, NH2 or is absent
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       (35)..(35)
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       Xaa = Ala, Asp, Arg, Glu, Lys, Gly, NH2 or is absent
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       (36)..(36)
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       Xaa = Pro, Ala, Lys, NH2 or is absent
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       Xaa = Pro, Ala, Lys, NH2 or is absent
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       (38)..(38)
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       Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
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Gln Ala Xaa Lys Glu Phe Ile Ala Trp Leu Xaa Lys Gly Gly Pro Xaa Page 23

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Xaa = Leu, Phe, Tyr, or Trp
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Xaa = Gly, Glu, Asp, or Lys
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Xaa = Ala, Val, Ile, or Leu

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x15642.ST25.txt
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        (45)..(45)
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Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Xaa Gly Xaa Xaa Xaa 20 25 30
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Xaa = Ser, Pro, or His
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<223>
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X15642.ST25.txt
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<223> Xaa = Ser, Arg, Thr, Trp, or Lys
<220>
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<222>
       (34)..(34)
<223>
       Xaa = Ser. or Glv
<220>
<221> MISC_FEATURE
<222> (35)..(35)
<223> Xaa = Ala, Asp, Arg, Glu, Lys, or Gly
<220>
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      (36) . . (36)
<223> Xaa = Pro, Ala, Lys, NH2 or is absent
<220>
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<222> (37)..(37)
<223> Xaa = Pro, Ala, Lys, NH2 or is absent
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<222> (38)..(38)
<223>
       Xaa = Pro, Ala, Arg, Lys, His, NH2 or is absent
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<222> (40)..(40).
<223> Xaa = His, Ser, Arg, Lys, NH2 or is absent
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<223> Xaa = His, Ser, Arg, Lys, NH2 or is absent
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       (42)..(42)
      Xaa = Lys, NH2, or is absent
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       (43)..(43)
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       (44)..(44)
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<221>
<222>
       (45)..(45)
Xaa = Lys, NH2 or is absent
<223>
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<400> 14
His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Gly Pro Xaa
<210>
<211>
       31
<212>
       PRT
<213>
       Artificial
<220>
<223>
       Synthetic construct
<220>
<221>
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       (1)..(1)
<223>
       Xaa = L-histidine, D-histidine, desamino-histidine,
2-amino-histidine, beta-hydroxy-
       histidine, homohistidine, alpha-fluoromethyl-histidine, or
       alpha-methyl-histidine
<220>
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       (2)..(2)
Xaa = Ala, Gly, Val, Leu, Ile, Ser orThr
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       (6)..(6)
<223>
       Xaa = Phe, Trp, Tyr
<220>
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       (10)..(10)
<223>
       Xaa = Val, Trp, Ile, Leu, Phe, or Tyr
<220>
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       (12)..(12)
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       Xaa = Ser, Trp, Tyr, Phe, Lys, Ile, Leu, Val
<220>
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       MISC_FEATURE
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       (13)..(13)
       Xaa = Tyr, Trp, or Phe
<223>
<220>
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       (14)..(14)
<223>
       xaa = Leu, Phe, Tyr, or Trp
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<220> <221>

MISC_FEATURE

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x15642.ST25.txt
<222>
        (16)..(16)
Xaa = Gly, Glu, Asp, Lys
<223>
<220>
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        (19)..(19)
<223>
        Xaa = Ala, Val, Ile, or Leu
<220>
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        (21)..(21)
Xaa = Glu, Ile, or Ala
<223>
<220>
        MISC_FEATURE (24)..(24)
<221>
<222>
<223>
        Xaa = Ala or Glu
<220>
<221>
<222>
        MISC_FEATURE
        (27)..(27)
Xaa = Val or Ile
<223>
<220>
        MISC_FEATURE
<221>
<222>
        (31)..(31)
Xaa = Gly, His, Lys, or NH2 or is absent
<223>
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Xaa Xaa Glu Gly Thr Xaa Thr Ser Asp Xaa Ser Xaa Xaa Xaa Glu Xaa
Gln Ala Xaa Lys Xaa Phe Ile Xaa Trp Leu Xaa Lys Gly Arg Xaa
<210>
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        31
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        Artificial
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<220>
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        Synthetic construct
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His Ala Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Lys Gly Arg Gly 20 25 30
<210>
        17
<211>
        39
<212>
        PRT
<213>
        Artificial
<220>
<223>
        Synthetic construct
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X15642.ST25.txt
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<210> 20 <211> 32 <212> PRT

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X15642.ST25.txt
<213>
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<220>
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        Synthetic construct
<220>
       MOD_RES (32)..(32) S-sulfonate (SSO3) is attached to the thiol of Cys at position 32
<221>
<222>
<223>
<400>
        20
His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Cys 20 \hspace{1cm} 25 \hspace{1cm} 30
<210>
        21
32
<211>
<212>
        PRT
<213>
       Artificial
<220>
<223>
       Synthetic construct
<400>
His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu 1
Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Lys
<210>
<211>
        22
32
<212>
        PRT
<213>
        Artificial
<220>
<223>
       Synthetic construct
<220>
<221>
<222>
        MOD_RES
        [32]..(32)
[32]..(32)
[3-(2-pyridy|dithio)propanamide]amide is attached to Lys at
position 32
<223>
<400>
        22
His Val Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Glu
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Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Ile Lys Gly Arg Gly Lys

x15642.ST25.txt <210> <211> <212> 23 39 PRT Heloderma suspectum <220> <221> <222> <223> MISC_FEATURE (1)..(39) Exendin-3 <400> 23 His Ser Asp Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 15 Glu Ala Val Arg Leu Phe Ile Glu Trp Leu Lys Asn Gly Gly Pro Ser Ser Gly Ala Pro Pro Pro Ser <210> <211> <212> <213> 24 39 PRT Heloderma suspectum <220> <221> <222> MISC_FEATURE (1)..(39) Exendin-4 <223> <400> 24 His Gly Glu Gly Thr Phe Thr Ser Asp Leu Ser Lys Gln Met Glu Glu 1 5 10 15

Ser Gly Ala Pro Pro Pro Ser